Selective Reduction of N-Substituted-3-carbamoyl Pyridinium Salts to the Corresponding Dihydropyridines Mediated by Low Valent Cobalt Complexes (Commemoration Issue Dedicated to Professor Yuzo Inouye on the Occasion of his Retirement)

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Selective Reduction of *N*-Substituted-3-carbamoyl Pyridinium Salts to the Corresponding Dihydropyridines Mediated by Low Valent Cobalt Complexes

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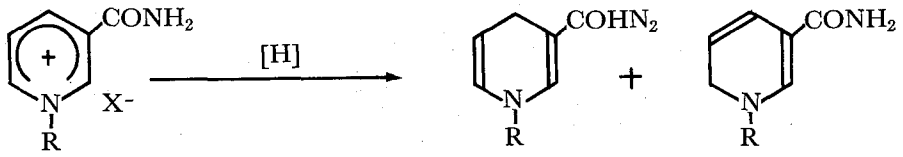
Catalytic or stoichiometric reduction of the title compound by Co(I) afforded *N*-substituted-3-carbamoyl-1, 4-dihydropyridine with high regioselectivity. An alkylocobalt complex is proposed as the reactive intermediate based on the isolation of substituted tetrahydrobipyridine.

KEY WORDS: Cobalt(I)/ Partial Reduction/ Catalytic

INTRODUCTION

N-Substituted-3-carbamoyl-1, 4-dihydropyridine (1) is a compound furnishing the fundamental framework of important coenzyme NADH and NADPH, and increasingly attracts attention of synthetic chemists as a mild reductant in organic and enzymatic-organic syntheses.[1] For the synthesis of dihydropyridines from pyridinium salts, the reduction by dithionite has been preferred because of convenience and the high regioselectivity to give 1, 4-dihydropyridines without producing the biologically inactive 1, 6-isomers. The main disadvantage of the reagent is, however, its reluctance to accept the chemical modification and the limited solubility in organic solvents.



The reduction of pyridinium salts by tetrahydroborate was reported to yield 1, 6-dihydropyridines as the major product,[2] and the electrochemical reduction generated dimers of dihydropyridines.[3] As for the transition metal catalyzed hydrogenation, a conventional hydrogenation catalyst such as platinum, which hydrogenates by the "hydride-insertion" mechanism,[4] brought about the overreduction to tetrahydropyridine and pipieridine.[5] Nevertheless, there are possibilities of a variety of mechanisms for the reduction by transition metal catalysts such as electron transfer and nucleophilic or radical addition of low valent metal complexes to the substrates.[6] In spite of the abundant reports on the redox reactions of transition metal complexes

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simulating natural redox systems,[7] clear examples of the non-"metal hydride" reduction of unsaturated substrates by transition metal complexes are few.[8] Now we found that pyridinium salts were reduced selectively to dihydropyridines by Co(I) complexes and that the reduction took place through an intermediate by the non-"metalhydride-insertion" mechanism as is reported in this manuscript.

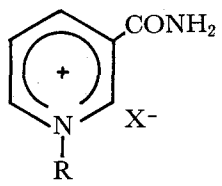
RESULTS

Stoichiometric reactions: The reduction of pyridinium salts by tetrahydroborate yields a mixture of 1, 4- and 1, 6-dihydropyridines with a low selectivity. However, when the reduction by tetrahydroborate was mediated by the cobalt complex, both the yield of dihydropyridines and the selectivity toward the 1, 4-isomer was affected. Thus, a mixture of BH_4^- and Co(I) complex, prepared by the reaction of Co(III) complex (2) with BH_4^-, was treated with pyridinium salts. Then a rapid color change occured from the characteristic blue of Co(I) to the yellow brown. Isolation of the product after 5 min of stirring gave the dihydropyridines in good yields. The selectivity toward the 1, 4-isomer was better than the reduction with BH_4^- alone although the effect was small in a certain case. The results are summarized in Table I. The selectivity was dependent on the ligands in cobalt complexes: electronreleasing piperidine tended to decrease the selectivity of the 1, 4-isomer, while replacement of equatorial methyl groups in 2a by phenyl groups brought about a small increase.

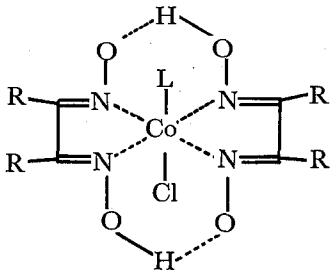
Table I. Reduction of Pyridinium Salts by Co(I)-BH_4[a]

Substrate	Complex	Solvent	Yield, %[b]	Selectivity, %[c]
1a	2a	H_2O	22 (24)	93 (80)
		CH_3OH	19	80
1b	2a	H_2O	70 (63)	70 (55)
		CH_3OH	72	70
1c		H_2O	80 (60)	73 (45)
		CH_3OH	56	64
		H_2O[d]	15	73
		CH_3OH[d]	25	68
1d		H_2O	85 (90)	57 (41)
1c	2b	CH_3OH	70	69
	2c	H_2O	60	74
	2d	CH_3OH	73	61
	2e	H_2O	19	66

a) Cobalt complex, 0.5 mmol; substrate, 0.25 mmol; $NaBH_4$, 0.5 mmol; NaOH, 1 mmol; Solvent, 20 ml; at 0°C under N_2. The yield is based on the amount of substrate used.
b) Values in the parentheses show the reduction by the use of BH_4^- only.
c) Selectivity of 3-carbamoyl-1, 4-dihydropyridine in dihydropyridines.
d) Solvent, 200 ml.



(1)



(2)

a: R=Pr X=Br
b: R=CH_2CH_2Ph X=Cl
c: R=CH_2Ph X=Cl
d: R=Ph X=Cl

a: R=CH_3 L=Pyridine
b: R=Ph L=Pyridine
c: R=CH_3 L=$P(Ph)_3$
d: R=CH_3 L=Piperidine
e: R=CH_3 L=$S(CH_3)_2$

When excess tetrahydroborate was removed from the solution of Co(I) by the addition of acetone, no organic product was isolated by the usual workup after a short reaction time (5 min) even though similar color change to give a brown solution was observed by the addition of pyridinium salt. However, bubbling of hydrogen gas through the brown solution for 12 h gave the dihydropyridines in good yields with a high regioselectivity of the 1, 4-isomer. In contrast, when the brown solution prepared from 1c was stirred for 12 h without bubbling of hydrogen gas, 1, 1′-dibenzyl-3, 3′-dicarbamoyl-1, 1′, 4, 4′-tetrahydro-4, 4′-bipyridine[3] was isolated in a 90% yield. The reduction of brown solution took place similarly in a short reaction period by using BH_4^- although the yield of dihydropyridines and the selectivity of the 1, 4-isomers decreased compared with the reduction by hydrogen. The results are listed in Table II.

Table II. Reduction of Pyridinium Salts with BH_4^--free Co(I) and the Hydrogen Source[a]

Substrate	Complex	Solvent	Procedure[b]	Yield, %	Selectivity, %
1a	2a	CH_3OH	A	53	95
			B	20	80
		H_2O	B	29	85
1c		CH_3OH	A	100	86
			B	82	65
		H_2O	B	65	55
	2b	CH_3OH	A	0	—

a) Cobalt complex, 0.5 mmol; Substrate, 0.25 mmol; $NaBH_4$, 0.5 mmol; NaOH, 1 mmol; Solvent, 20 ml; and acetone, 0.4 ml.

b) Procedure A: Bubbling hydrogen gas for 12 h at room temperature.
Procedure B: Stirring 5 min after the addition of 0.5 mmol of $NaBH_4$ at 0°C.

Catalytic reductions: For the purpose of synthesis, the catalytic reduction is more valuable than the stoichiometric reaction. Although the reduction under the atmospheric pressure of hydrogen did not proceed catalytically because of slow rate of the reduction of cobalt complexes, a smooth reaction was effected under the increased pressure of hydrogen. The yields of dihydropyridines were moderate but the selectivity

was very good to see up to 100% for 1a. Maximum catalytic turnover obtained was 23 for the reduction of 1c although the reaction conditions were not yet optimized. The results are listed in Table III. Under a high pressure of hydrogen, overreduction took place in some extent. The complex of diphenylglyoxime (2b) did not mediate the reduction under atmospheric pressure of hydrogen and the reaction was not clean under the 20 atm of hydrogen. Reduction of 1d with 2a was also slow.

Table III. Catalytic Hydrogenation of Pyridinium Salts[a)]

Substrate	Catalyst	Base	Pressure, atm	Yield, %	Selectivity, %
1a	2a	NaOH (1)	80	45	100
		Na_2CO_3 (2)	20	47	100
1c		Na_2CO_3 (1)	80	71	90
		$NaHCO_3$ (1)	20	69	83
		Na_2CO_3 (20)	20	58	89[b)]
		Na_2CO_3 (1)	20	20	93[c)]
1d		Na_2CO_3 (2)	20	0	—

a) Catalyst, 0.1 mmol; Substrate, 1 mmol; Base, 1–2 mmol (specified in the pharentheses); CH_3OH, 150 ml; overnight.
b) Catalyst, 0.5 mmol; Substrate, 20 mmol; Base, 20 mmol; CH_3OH, 150 ml; 3 days.
c) In acetonitrile (100 ml).

DISCUSSION

The catalytic hydrogenation in the presence of transition metal species is a process of wide use in laboratories as well as in industries. The generally accepted mechanism of the catalysis involves the activation of hydrogen by the metal to give a metal hydride and the subsequent transfer of the hydride to unsaturated substrates by the insertion and reductive elimination reactions.[4)] However, the application of these hydrogenation catalysts to the partial reduction of pyridinium salts has been unsuccessful because the dihydropyridine, which is the primary product, is more reactive than the substrate itself under the reaction conditions.[2)] In fact, hydrogenation in the presence of a catalytic amount of $RhCl(PPh_3)_3$ gave *N*-substituted-3-carbamoyltetrahydropyridines in good yields.[9)] This result suggests that the reduction by non-"hydride insertion" mechanism would be more fruitful for the partial reduction of pyridinium salts. In this contexst, the low valent cobalt complex is an attractive reagent judging from its highly nucleophilic character noted as the "super nucleophile".[10)]

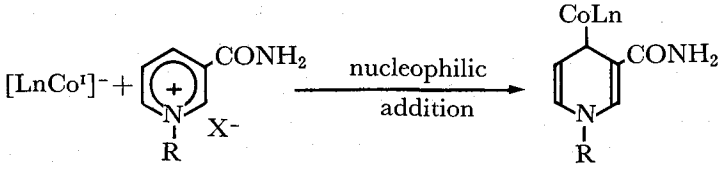
The reduction of cobalt complexes 2 with tetrahydroborate[11)] or hydrogen yields acidic cobalt hydrides (3). Under the alkaline reaction conditions employed for the present reaction, 3 is expected to exist almost exclusively in the form of conjugate base,[11)] which would react with the substrate to give an intermediate complex (4).

$$LnCo^{III}X + [H^-] \longrightarrow \underset{(3)}{LnCo^{III}H} + X^- \qquad (1)$$

$$B + \underset{(3)}{LnCo^{III}H} \rightleftarrows [LnCo^{I}]^- + BH^+ \qquad (2)$$

In support of the proposal, the reduction of pyridinium salts did not take place in the absence of a base.

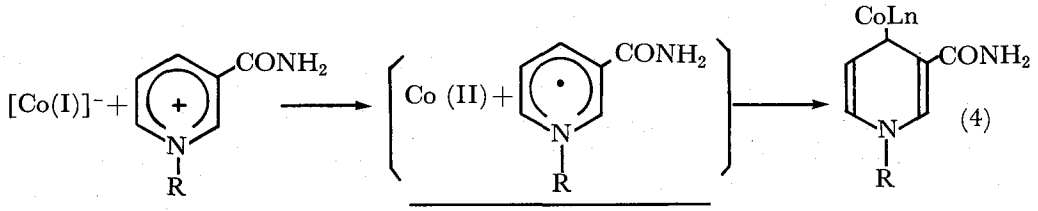
Two alternative mechanisms can be proposed for the addition of Co(I) to the substrate: a direct nucleophilic addition of Co(I) to the substrate (Eq. 3)[12],



(3)

(4)

or an initial electron transfer form Co(I)[13] to pyridinium salt, followed by the radical combination of the generated two radical species within the solvent cage (Eq. 4)



(4)

(4)

Spectrophotometric analyses of the reaction of 1c with the BH_4^--free Co(I) complex prepared from 2a showed a rapid decrease of the absorption at 650 nm, which is characteristic for Co(I), by the addition of pyridinium salt with a concominant

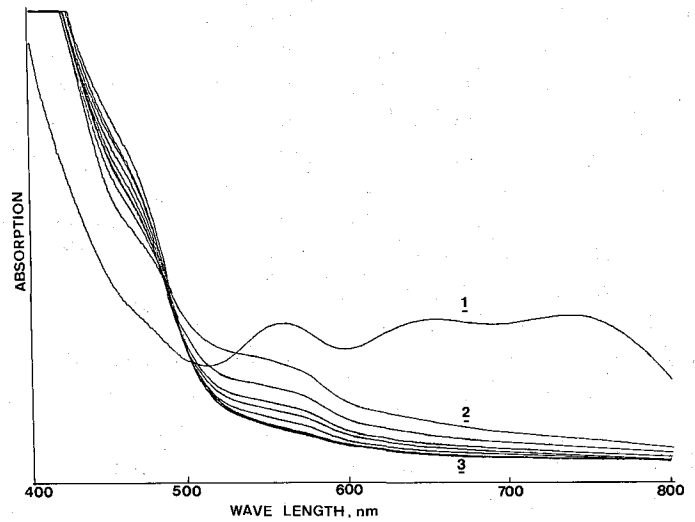


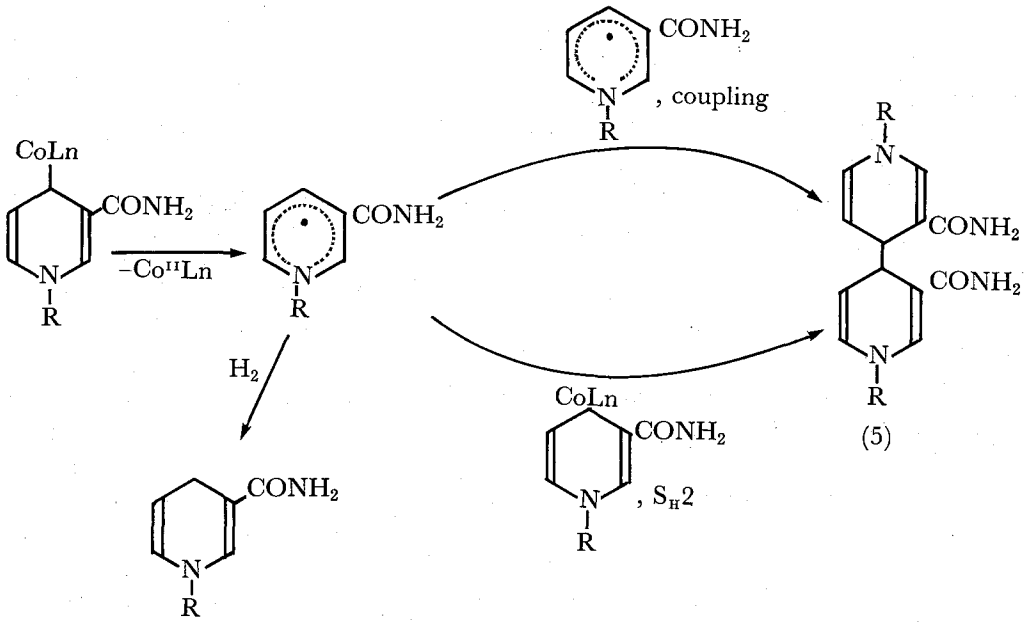
Fig. 1. Time dependent electronic spectra of the reaction of 1c with Co(I) prepared from 2a.

(1); Co(I) prepared from 2a.

(2)–(3); Co(I)+1c. 1 min, 15 min, 30 min, 60 min, 120 min, and 240 min after mixing, respectively.

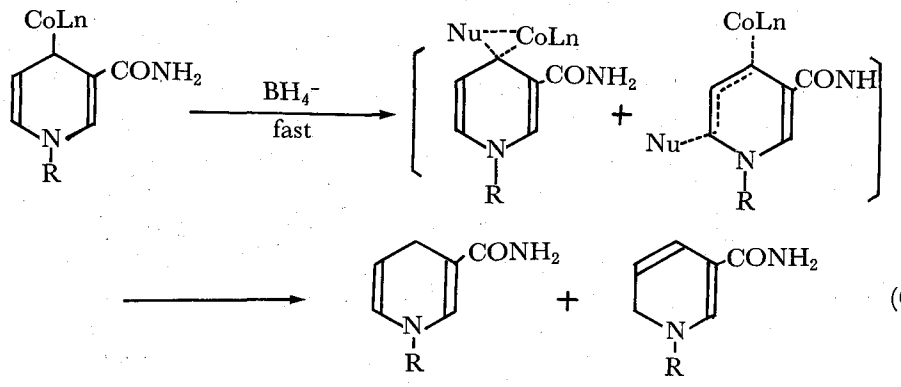
increase of the absorption around 460 nm (Fig. 1). The latter absorption was assigned to the alkyl cobalt complexes on the basis of the data in literature.[12,14]

Since an allylcobalt complex dissociates into an allyl radical and Co(II),[15] the isolation of a dimer, 1, 1′-dibenzyl-3, 3′-dicarbamoyl-1, 1′, 4, 4′-tetrahydro-4, 4′-bipyridine, (5), after a long reaction period strongly supports the presence of complex 4. Formation of dimer 5 would take place either by the coupling of two pyridinyl radicals[16] or by the S_H2-type reaction between a pyridinyl radical and complex 4.[17] Under the atmosphere of hydrogen, the pyridinyl radical would react with hydrogen to give the dihydropyridine.



The results indicate that the rapid hydrogenation of pyridinium salts by BH_4^- proceeded less selectively to give a mixture of 1, 4- and 1, 6-isomers but the slow hydrogenation or dimerization resulted in the overwhelming selectivity toward the 1, 4-isomer.[18] Since the thermal dissociation of cobalt-carbon bond is not a rapid process,[15] the big difference of two hydrogen sources in the reactivity and selectivity indicates the presence of two alternative processes in the hydrogenation of the intermediate complex 4. We tentatively propose here an ionic mechanism for the reaction with tetrahydroborate. Nucleophilic substitution of the allylmetal complexes has many precedents.[19]

The observed selectivity in the reduction by Co(I)-BH_4^- would be interpreted on the basis of the proposed mechanism followingly. An electron-withdrawing ligand decreases the electron density of cobalt metal and facilitate the approach of a nucleophile toward the metal, increasing the selectivity of 1, 4-isomer. The opposite situation holds for the electron releasing ligands. The electron-withdrawing ligands may also serve for stabilizing the cobalt-carbon bond from unimolecular dissociation,



and decrease the rate of reduction by molecular hydrogen.

EXPERIMENTAL

Materials: Pyridinium salts[20] and cobalt complexes[21] were prepared by the literature methods. Other compounds were reagent grade and used without further purification.

As Co(I) species are sensitive to dioxygen, experiments were carried out under nitrogen or argon atmosphere and all the solvents in the stoichiometric reactions were carefully deaerated before use.

Reduction of pyridinium salts with Co(I) and BH_4^- To an ice-cooled solution of Co(III) complex (0.5 mmol) in 20 ml of methanol was added a solution of $NaBH_4$ (0.5 mmol) and NaOH (1 mmol) in water (1ml). The color of the solution turned dark blue immediately. The solution was then stirred for 20 min at 0°C to ensure the formation of Co(I). An aqueous solution of pyridinium salt (0.25 mmol) was then added to the ice-cooled solution of Co(I) through a syringe and the mixture was stirred for 5 min. Methanol was removed from the reaction mixture and the residue was extracted by ether. The organic layer was concentrated to give the product, which was analyzed by NMR.

Reaction of pyridinium salts with a stiochiometric amount of Co(I) followed by the reduction with the hydrogen source: Co(I) was prepared similarly as above except for the addition of 0.4 ml of acetone to the generated solution of Co(I) to decompose excess BH_4^-. Pyridinium salt was then added to BH_4^--free Co(I) and the reduction was completed by bubbling hydrogen gas for 12 h under stirring, or by the addition of 0.5 mmol of $NaBH_4$ in water followed by stirring the mixture for 5 min. Isolation and analyses of the products were carried out similarly as described above. Stirring the reaction mixture of BH_4^--free Co(I) and 1c for 12 h at room temperature gave 5 in a 90% yield after usual workup.

Catalytic reaction: In a typical procedure, pyridinium salt (1 mmol), base (1–2 equivalent), and the catalyst (1 mmol) were dissolved in 100 ml of methanol and the solution was placed in a 300-ml stainlesssteel autoclave. The autclave was shaked at room temperature under the specified pressure. Methods for isolation and analyses of products were the same as described above.

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